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<p>(21) International Application Number: PCT/US96/20327</p> <p>(22) International Filing Date: 20 December 1996 (20.12.96)</p> <p>(30) Priority Data: 60/009,367 29 December 1995 (29.12.95) US</p> <p>(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): ALI, Fadia, E. [US/US]; 5 North Green Acre Drive, Cherry Hill, NJ 08003 (US). BONDINELL, William, E. [US/US]; 1512 Franklin Lane, Wayne, PA 19087 (US). KEENAN, Richard, M. [US/US]; 796 Bass Cove, Malvern, PA 19355 (US). KU, Thomas, Wen, Fu [-/US]; 1413 Southwind Way, Dresher, PA 19025 (US). MILLER, William, H. [US/US]; 333 Fell Lane, Schwenksville, PA 19473 (US). SAMANEN, James [US/US]; 145 Jug Hollow Road, Phoenixville, PA 19460 (US).</p>		<p>(74) Agents: McCARTHY, Mary, E. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).</p> <p>(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
(54) Title: VITRONECTIN RECEPTOR ANTAGONISTS		
<p>(57) Abstract</p> <p>Compounds of formula (I) are disclosed, wherein: A is a fibrinogen antagonist template; W is a linking moiety of the form $-(CHR^a)_n-U-(CHR^b)_m-V-$; Q^1, Q^2, Q^3 and Q^4 are independently N or C-R^y, provided that no more than one of Q^1, Q^2, Q^3 and Q^4 is N; R^1 is H or C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar-C_{0-6}alkyl; R^2 is H or C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar-C_{0-6}alkyl; R^3 is R^2, $-C(O)R^2$ or $-C(O)OR^2$; R^4 is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl-$U'-C_{1-6}$alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl-$U'-C_{1-6}$alkyl or Ar-C_{0-6}alkyl-$U'-C_{1-6}$alkyl; R^y is H, halo, $-OR^2$, $-SR^2$, $-CN$, $-NR^2R^3$, $-NO_2$, $-CF_3$, $CF_3S(O)_2-$, $-CO_2R^2$, $-COR^2$ or $-CONR^2$, or C_{1-6}alkyl optionally substituted by halo, $-OR^2$, $-SR^2$, $-CN$, $-NR^2R^3$, $-NO_2$, $-CF_3$, $R^1S(O)_2-$, $-CO_2R^2$, $-COR^2$ or $-CONR^2$; U and V are absent or CO, CR^2, $C(=CR^2)$, $S(O)_2$, O, NR^2, CR^2OR^2, $CR^2(OR^2)CR^2$, $CR^2CR^2(OR^2)$, $C(O)CR^2$, $CR^2C(O)$, $CONR^2$, NR^2CO, $OC(O)$, $C(O)O$, $C(S)O$, $OC(S)$, $C(S)NR^2$, $NR^2C(S)$, $S(O)_2NR^2$, $NR^2S(O)_2N=N$, NR^2NR^2, NR^2CR^2, NR^2CR^2, CR^2O, OCR^2, $CR^2=CR^2$, $C\equiv C$, Ar or Het; a is 0, 1, 2 or 3; b is 0, 1 or 2; c is 0, 1 or 2; r is 0, 1 or 2; and u is 0 or 1; or pharmaceutically acceptable salts thereof, which are vitronectin receptor antagonists useful in the treatment of osteoporosis.</p> <div style="text-align: center;"> <p>(I)</p> </div>		

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TITLE

Vitronectin Receptor Antagonists

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FIELD OF THE INVENTION

This invention relates to pharmaceutically active compounds which inhibit the vitronectin receptor and are useful for the treatment of diseases wherein inhibition of the vitronectin receptor is indicated, such as inflammation, cancer, angiogenesis, atherosclerosis, restenosis, and diseases wherein bone resorption is a factor.

10

BACKGROUND OF THE INVENTION

Integrins are a superfamily of cell adhesion receptors, which are transmembrane glycoproteins expressed on a variety of cells. These cell surface adhesion receptors include gpIIb /IIIa, the fibrinogen receptor, and $\alpha_v\beta_3$, the vitronectin receptor. The fibrinogen receptor gpIIb /IIIa is expressed on the platelet surface and it mediates platelet aggregation and the formation of a hemostatic clot at the site of a bleeding wound. Philips, *et al.*, *Blood.*, **1988**, 71, 831.

The vitronectin receptor $\alpha_v\beta_3$ is expressed on a number of cells, including endothelial, smooth muscle, osteoclast, and tumor cells, and, thus, it has a variety of functions. The $\alpha_v\beta_3$ receptor expressed on the membrane of osteoclast cells is believed to play a role in the bone resorption process and contribute to the development of osteoporosis. Ross, *et al.*, *J. Biol. Chem.*, **1987**, 262, 7703; Fisher, *et al.*, *Endocrinology* **1993**, 132, 1411; Bertolini *et al.*, *J. Bone Min. Res.*, 6, Sup. 1, S146, 252; EP 528 587 and 528 586. The $\alpha_v\beta_3$ receptor expressed on human aortic smooth muscle cells stimulates their migration into neointima, which leads to the formation of atherosclerosis and restenosis after angioplasty. Brown, *et al.*, *Cardiovascular Res.*, **1994**, 28, 1815. Additionally, a recent study has shown that a $\alpha_v\beta_3$ antagonist is able to promote tumor regression by inducing apoptosis of angiogenic blood vessels. Brooks, *et al.*, *Cell*, **1994**, 79, 1157. Thus, agents that would block the vitronectin receptor would be useful in treating diseases mediated by this receptor, such as osteoporosis, atherosclerosis, restenosis and cancer.

Alig et al., EP 0 381 033, Hartman, et al., EP 0 540,334, Blackburn, et al., WO 93/08174, Bondinell, et al., WO 95/18619, Bondinell, et al., WO 94/14776, Blackburn, et al. WO 95/04057, Egbertson, et al, EP 0 478 328, Sugihara, et al. EP 529,858, Porter, et al., EP 0 542 363, and Fisher, et al., EP 0 635 492, and many others disclose certain
5 compounds that are useful for selectively inhibiting the fibrinogen receptor.
PCT/US95/08306, filed June 29, 1995 (SmithKline Beecham Corp.) and
PCT/US95/08146 filed June 29, 1995 (SmithKline Beecham Corp.) disclose
vitronectin receptor selective antagonists. However, there are few reports of compounds
which are potent vitronectin receptor antagonists. It has now been discovered that certain
10 appropriately substituted amino pyridine compounds are potent inhibitors of the
vitronectin receptor. In particular, it has been discovered that the amino pyridine moiety
may be combined with a fibrinogen atagonist template to prepare compounds which are
more potent inhibitors of the vitronectin receptor than the fibrinogen receptor.

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SUMMARY OF THE INVENTION

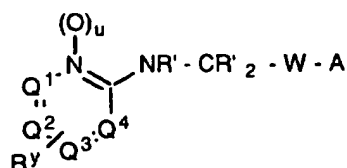
This invention comprises compounds of the formula (I) as described hereinafter,
which have pharmacological activity for the inhibition of the vitronection receptor and are
useful in the treatment of inflammation, cancer, cardiovascular disorders, such as
atherosclerosis and restenosis, and diseases wherein bone resorption is a factor, such as
20 osteoporosis.

This invention is also a pharmaceutical composition comprising a compound
according to formula (I) and a pharmaceutically acceptable carrier.

This invention is also a method of treating diseases which are mediated by the
vitronectin receptor. In a particular aspect, the compounds of this invention are useful for
25 treating atherosclerosis, restenosis, inflammation, cancer and osteoporosis.

DETAILED DESCRIPTION

This invention comprises novel compounds which are more potent inhibitors of
the vitronectin receptor than the fibrinogen receptor. The compounds of the instant
30 invention comprise a fibrinogen receptor antagonist template that is linked to an
optionally substituted 2-pyridyl-amine moiety according to formula (I):



(I)

wherein

A is a fibrinogen antagonist template;

5 W is a linking moiety of the form $-(\text{CHR}^g)_a-\text{U}-(\text{CHR}^g)_b-\text{V}-$;

Q^1 , Q^2 and Q^3 are independently N or C-R^y , provided that no more than one of Q^1 , Q^2 , Q^3 and Q^4 is N;

R' is H or C_{1-6} alkyl, C_{3-7} cycloalkyl- C_{0-6} alkyl or Ar-C_{0-6} alkyl

R^g is H or C_{1-6} alkyl, Het- C_{0-6} alkyl, C_{3-7} cycloalkyl- C_{0-6} alkyl or Ar-C_{0-6} alkyl;

10 R^k is R^g , $-\text{C}(\text{O})\text{R}^g$ or $-\text{C}(\text{O})\text{OR}^g$

R^i is H, C_{1-6} alkyl, Het- C_{0-6} alkyl, C_{3-7} cycloalkyl- C_{0-6} alkyl, Ar-C_{0-6} alkyl, Het- C_{0-6} alkyl- U' - C_{1-6} alkyl, C_{3-7} cycloalkyl- C_{0-6} alkyl- U' - C_{1-6} alkyl or Ar-C_{0-6} alkyl- U' - C_{1-6} alkyl;

R^y is H, halo, $-\text{OR}^g$, $-\text{SR}^g$, $-\text{CN}$, $-\text{NR}^g\text{R}^k$, $-\text{NO}_2$, $-\text{CF}_3$, $\text{CF}_3\text{S}(\text{O})_r$, $-\text{CO}_2\text{R}^g$, $-\text{COR}^g$ or

$-\text{CONR}^g_2$, or C_{1-6} alkyl optionally substituted by halo, $-\text{OR}^g$, $-\text{SR}^g$, $-\text{CN}$, $-\text{NR}^g\text{R}^k$,

15 $-\text{NO}_2$, $-\text{CF}_3$, $\text{R}'\text{S}(\text{O})_3-$, $-\text{CO}_2\text{R}^g$, $-\text{COR}^g$ or $-\text{CONR}^g_2$;

U and V are absent or CO, CR^g_2 , $\text{C}(\text{=CR}^g_2)$, $\text{S}(\text{O})_c$, O, NR^g , CR^gOR^g , $\text{CR}^g(\text{OR}^k)\text{CR}^g_2$, $\text{CR}^g_2\text{CR}^g(\text{OR}^k)$, $\text{C}(\text{O})\text{CR}^g_2$, $\text{CR}^g_2\text{C}(\text{O})$, CONR^i , NR^iCO , $\text{OC}(\text{O})$, $\text{C}(\text{O})\text{O}$, $\text{C}(\text{S})\text{O}$, $\text{OC}(\text{S})$, $\text{C}(\text{S})\text{NR}^g$, $\text{NR}^g\text{C}(\text{S})$, $\text{S}(\text{O})_2\text{NR}^g$, $\text{NR}^g\text{S}(\text{O})_2$, $\text{N}=\text{N}$, NR^gNR^g , NR^gCR^g_2 , NR^gCR^g_2 , CR^g_2O , OCR^g_2 , $\text{CR}^g=\text{CR}^g$, $\text{C}\equiv\text{C}$, Ar or Het;

20 a is 0, 1, 2 or 3;

b is 0, 1 or 2;

c is 0, 1 or 2;

u is 0 or 1;

and pharmaceutically acceptable salts thereof.

25 Preferably, Q^1 , Q^2 , Q^3 and Q^4 are all CH, and u is 0.

Suitably, R' is H and R'' is H or C_{1-4} alkyl.

Suitably, W is $-(\text{CHR}^g)_a-\text{CONR}^i-$ or $-(\text{CHR}^g)_a-\text{NR}^i\text{CO}-$

A fibrinogen receptor antagonist is an agent that inhibits the binding of fibrinogen to the platelet-bound fibrinogen receptor GPIIb-IIIa. Many fibrinogen antagonists are

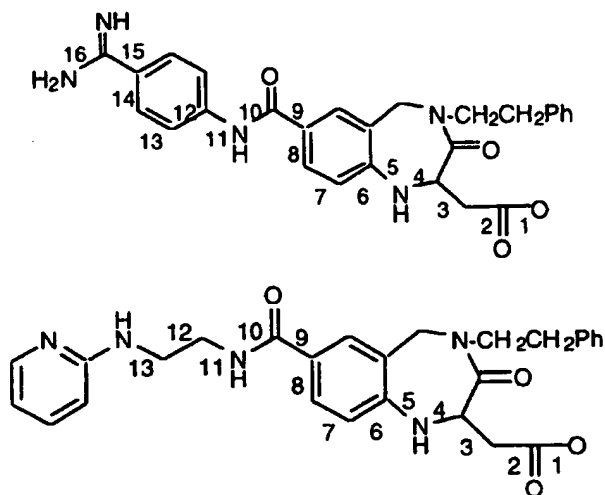
30 known to the art. As used herein, the term "fibrinogen receptor antagonist template"

means the core structure of a fibrinogen receptor antagonist, said core containing an acidic group and being linked to an organic group substituted with a basic nitrogen moiety. Typically, the core structure adds some form of rigid spacing between the acidic moiety and the basic nitrogen moiety, and contains one or more ring structures or amide bonds to effect this. It is preferred that about twelve to fifteen, more preferably thirteen or fourteen, intervening covalent bonds via the shortest intramolecular path will exist between the acidic group of the fibrinogen receptor antagonist template and nitrogen of the *o*-amino substituent on the pyridine moiety in formula (I). It is an object of this invention that a fibrinogen receptor antagonist is converted to a vitronectin receptor antagonist by replacing the basic nitrogen group in a fibrinogen receptor antagonist with an optionally substituted pyrid-2-yl-amino group. In addition, the number of intervening covalent bonds between the acidic moiety and the nitrogen of the *o*-amino substituent on the pyridine ring will be about two to five, preferably three or four, covalent bonds shorter than the number of intervening covalent bonds between the acidic moiety and the basic nitrogen group of the fibrinogen antagonist. The identity of the linking moiety W may be chosen to obtain the proper spacing between the acidic moiety of the fibrinogen antagonist template and the nitrogen atom of the pyridine. Generally, a fibrinogen antagonist will have an intramolecular distance of about 16 angstroms between the acidic moiety (e.g., the atom which gives up the proton or accepts the electron pair) and the basic moiety (e.g., which accepts a proton or donates an electron pair), while the vitronectin antagonist will have about 14 angstroms between the respective acidic and basic centers.

For purposes of illustration, using the 7-2,3,4,5-tetrahydro-3-oxo-4-methyl-benzodiazepine fibrinogen antagonist template disclosed in WO 93/08174 as a suitable fibrinogen antagonist template, the compound (R,S)-7-[[[4-(aminoiminomethyl)phenyl]amino]carbonyl]-4-(2-phenylethyl)-1,3,4,5-tetrahydro-3-oxo-2H-1,4-benzodiazepine-2-acetic acid, which is potent and selective fibrinogen antagonist, is converted to a potent and selective vitronectin receptor antagonist by replacing the 4-(aminoiminomethyl)phenyl moiety with the (pyrid-2-yl)ethyl moiety. As illustrated below in Figure 1, in the former case, there are sixteen intervening covalent bonds between the acidic moiety and the basic moiety; in the fibrinogen antagonist whereas, in

the latter case there are 13 intervening covalent bonds in the vitronectin antagonist of this invention.

Figure 1



5

In fact the 4-(aminoiminomethyl)phenyl moiety is a common substituent on fibrinogen antagonist templates known to the art, and simple replacement of this moiety with an optionally substituted (pyrid-2-yl)aminoethyl moiety may serve as guide to converting compounds having known fibrinogen antagonist templates into vitronectin receptor antagonists.

Also included in this invention are pharmaceutically acceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*. In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the *cis* (*Z*) and *trans* (*E*) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, such as and each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or locked in one form by appropriate substitution with R'.

The compounds of formula (I) inhibit the binding of vitronectin and other RGD-containing peptides to the vitronectin ($\alpha_v\beta_3$) receptor. Inhibition of the vitronectin

receptor on osteoclasts inhibits osteoclastic bone resorption and is useful in the treatment of diseases wherein bone resorption is associated with pathology, such as osteoporosis. Additionally, since the compounds of the instant invention inhibit vitronectin receptors on a number of different types of cells, said compounds would be useful in the treatment of
5 inflammation and cardiovascular diseases, such as atherosclerosis and restenosis, and would be useful as anti-metastatic and antitumor agents.

Table I, below, describes certain fibrinogen receptor antagonists, whose core structures are useful in carrying out the instant invention. Reference should be made to
10 the patent applications and other publications for their full disclosures, including the methods of preparing said templates and specific compounds embodying said templates. The entire disclosure of the noted patent applications and other publications is incorporated herein by reference as though fully set forth. The list following is not intended to limit the scope of the present invention, but only to illustrate certain known
15 templates.

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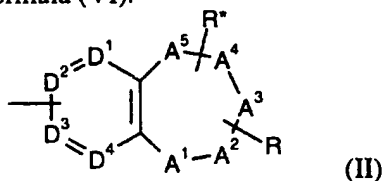
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20 In one particular embodiment, the fibrinogen receptor antagonist template A is the fused 6/7 ring bicyclic ring defined in Bondinell, et al., WO 93/00095, published January 7, 1993, as defined by sub-formula (VI):



wherein

25 A¹ to A⁵ form an accessible substituted seven-membered ring, which may be saturated or unsaturated, optionally containing up to two heteroatoms chosen from the group of O, S and N wherein S and N may be optionally oxidized;

D¹ to D⁴ form an accessible substituted six membered ring, optionally containing up to two nitrogen atoms;

30 R is at least one substituent chosen from the group of R⁷, or Q-C₁₋₄alkyl, Q-C₂₋₄alkenyl, Q-C₂₋₄alkynyl, optionally substituted by one or more of =O, R¹¹ or R⁷;

R* is H, Q-C₁₋₆alkyl, Q-C₁₋₆oxoalkyl, Q-C₂₋₆alkenyl, Q-C₃₋₄oxoalkenyl, Q-C₃₋₄oxoalkynyl, Q-C₂₋₄alkynyl, C₃₋₆cycloalkyl, Ar or Het, optionally substituted by one or more of R¹¹;

- Q is H, C₃₋₆cycloalkyl, Het or Ar;
 R⁷ is -COR⁸, -COCR'₂R⁹, -C(S)R⁸, -S(O)_mOR', -S(O)_mNR'R'', -PO(OR'),
 -PO(OR')₂, -B(OR')₂, -NO₂ and Tet;
 R⁸ is -OR', -NR'R'', -NR'SO₂R', -NR'OR', -OCR'₂C(O)OR', -OCR'₂OC(O)-R',
 5 -OCR'₂C(O)NR'₂, CF₃ or AA¹;
 R⁹ is -OR', -CN, -S(O)_rR', S(O)_mNR'₂, -C(O)R' C(O)NR'₂ or -CO₂R';
 R¹¹ is H, halo, -OR¹², -CN, -NR'R¹², -NO₂, -CF₃, CF₃S(O)_r, -CO₂R', -CONR'₂,
 Q-C₀₋₆alkyl-, Q-C₁₋₆oxoalkyl-, Q-C₂₋₆alkenyl-, Q-C₂₋₆alkynyl-, Q-C₀₋₆alkyloxy-, Q-C₀₋₆
 6alkylamino- or Q-C₀₋₆alkyl-S(O)_r;
 10 R¹² is R', -C(O)R', -C(O)NR'₂, -C(O)OR¹⁵, -S(O)_mR' or S(O)_mNR'₂;
 R¹³ is R', -CF₃, -SR', or -OR';
 R¹⁴ is R', C(O)R', CN, NO₂, SO₂R' or C(O)OR¹⁵;
 R¹⁵ is H, C₁₋₆alkyl or Ar-C₀₋₄alkyl;
 R' is H, C₁₋₆alkyl, C₃₋₇cycloalkyl-C₀₋₄alkyl or Ar-C₀₋₄alkyl;
 15 R'' is R', -C(O)R' or -C(O)OR¹⁵;
 R''' is R'' or AA²;
 AA¹ is an amino acid attached through its amino group and having its carboxyl
 group optionally protected, and AA² is an amino acid attached through its carboxyl
 group, and having its amino group optionally protected;
 20 m is 1 or 2;
 n is 0 to 3;
 p is 0 or 1; and
 t is 0 to 2; or
 pharmaceutically acceptable salts thereof.
 25 With reference to formula (II), suitably,
 A¹ is CR¹R^{1'}, CR¹, NR¹, N, O or S(O)_x;
 A² is CR²R^{2'}, CR², NR²;
 A³ is CR³R^{3'}, CR³, NR³, N, O or S(O)_x;
 A⁴ is CR⁴R^{4'}, CR⁴, NR⁴, or N;
 30 A⁵ is CR⁵R^{5'}, CR⁵, NR⁵, N, O or S(O)_x;
 D¹-D⁴ are CR¹¹, CR⁶ or N;
 R¹ and R^{1'} are R* or R, or together are =O;
 R² and R^{2'} are R*, R or =O;
 R³ and R^{3'} are R*, R or =O;
 35 R⁴ and R^{4'} are R*, R or =O;
 R⁵ and R^{5'} are R*, R or =O; and
 x is 0 to 2.

More suitably, A^1 is CR^1R^1 , CR^1 , NR^1 , N , O or S ; A^2 is CR^2R^2 , NR^2 or CR^2 ; A^3 is CR^3R^3 ; A^4 is CR^4R^4 , CR^4 , NR^4 , or N ; A^5 is CR^5R^5 , CR^5 , NR^5 , N , O ; $D^1 - D^4$ are CH ; R^2 or R^4 are R ; R^3, R^3' and R^5, R^5' are $=O$ or R^*, H .

Preferably, A^1 is CHR^1 , CR^1 , NR^1 , N or S ; A^2 is CR^2 or CR^2R^2 ; A^3 is CR^3R^3 ; A^4 is CR^4R^4 or NR^4 ; A^5 is CR^5R^5 , and $D^1 - D^4$ are CH .

In one embodiment, A^1 is CR^1 , A^2 is CR^2 , A^3 is $C=O$, A^4 is NR^4 and A^5 are CHR^5 .

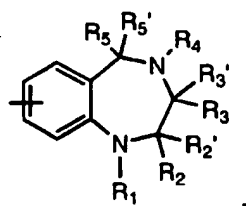
In another embodiment, A^1 is NR^1 , A^2 is $CHCR^2$, A^3 is CR^3R^3 , A^4 is NR^4 , and A^5 are $C=O$.

In yet another embodiment, A^1 and A^4 are $C=O$, A^2 is NR^2 , A^3 is CHR^3 and A^5 is NR^5 .

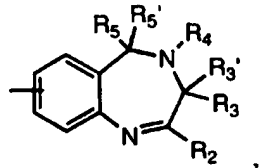
In a preferred embodiment, A^1 is NR^1 , A^2 is CHR^2 , A^3 is $C=O$, A^4 is NR^4 and A^5 is CHR^5 .

Representative sub-formulas of (II) are given by each of formulas (IIa)-(IIIi)

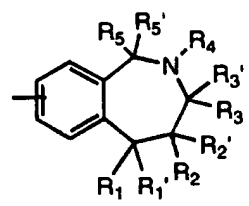
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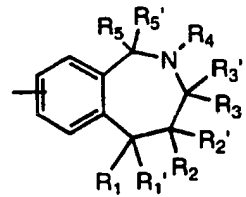
(IIa)



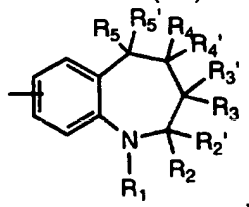
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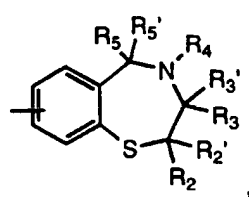
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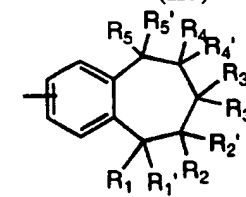
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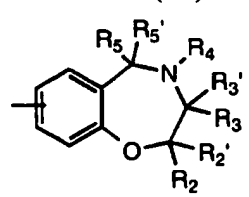
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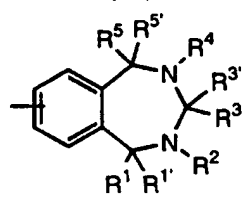
(IIIf)



(IIg)

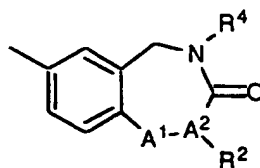


(IIh)



(IIIi)

A preferred template is given by formula (III):



(III)

wherein

A¹-A² is NR¹-CH, NC(O)R³-CH, N=C, CR¹=C, CHR¹-CH, O-CH or S-CH;

5 R¹ is H, C₁-₆ alkyl or benzyl;

R² is (CH₂)qCO₂H;

R⁴ is H, C₁-₆alkyl, Ar-C₀-₆alkyl, Het-C₀-₆alkyl, or C₃-₆cycloalkyl-C₀-₆alkyl; and

q is 1, 2 or 3.

10 Preferably A¹-A² is NH-CH and R² is CH₂CO₂H. Suitably, R³ is methyl and W (as defined in formula (I)) is CH₂NR'CO. Suitably R' is substituted by NHR', CN, CO₂H, biotin, benzimidazole or optionally substituted phenyl.

Specific examples of vitronectin antagonists employing this template are:

(S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[2-(pyridinyl)amino]ethyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;

15 (S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[(1-oxo-2-pyridinyl)amino]ethyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-3-oxo-7-[[[2-[2-(pyridinyl)amino]ethyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;

20 (S)-2,3,4,5-Tetrahydro-3-oxo-7-[[[2-[2-(pyridinyl)amino]ethyl]amino]carbonyl]-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-3-oxo-4-(phenylethyl)-7-[[[2-[2-(pyridinyl)amino]ethyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-4-methyl-7-[[[2-[2-(6-methylpyridinyl)amino]ethyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

25 (S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[2-(pyridinyl)amino]ethyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;

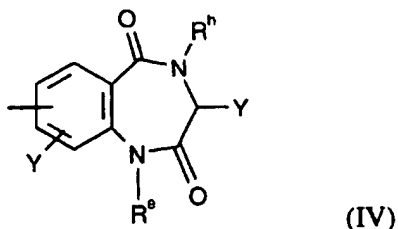
(±)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[2-(pyrimidinyl)amino]ethyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;

30 (±)-2,3,4,5-Tetrahydro-4-methyl-7-[[[2-[(6-methyl-3-pyridazinyl)amino]ethyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid; and

(±)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[3-(pyridazinyl)amino]ethyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid.

A preferred compound is (S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[2-[2-(pyridinyl)amino]ethyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid.

Another embodiment of a benzodiazepine fibrinogen receptor template A is represented by the 1,4-benzodiazepine 2,5-dione of sub-formula (IV);



wherein:

- 5 Y is H, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, F, Cl, Br, I, CF₃, OR^f, S(O)_kR^f, COR^f, NO₂, N(R^f)₂, CO(NR^f)₂, CH₂N(R^f)₂, methylenedioxy, CN, CO₂R^f, OC(O)R^f, or NHC(O)R^f; and

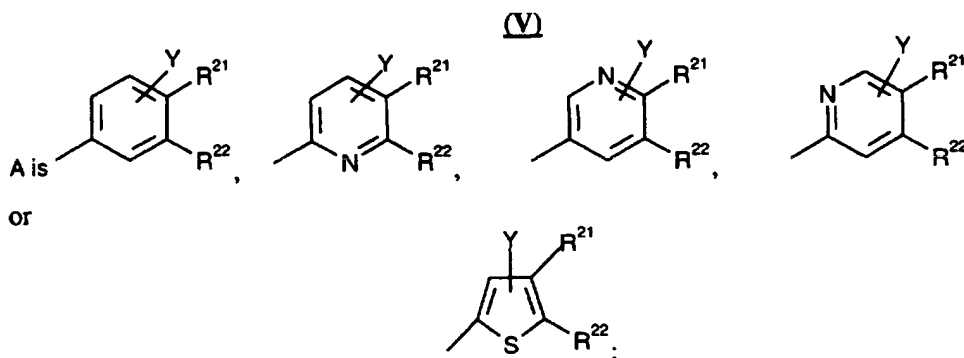
R^h is (CH₂)_qCO₂R^f.

Suitably R^h is CH₂CH₂CO₂H.

- 10 Entries (V)-(XV) in Table II summarize other illustrative fibrinogen receptor templates that are included within the scope of the present invention:

Table II

15



wherein:

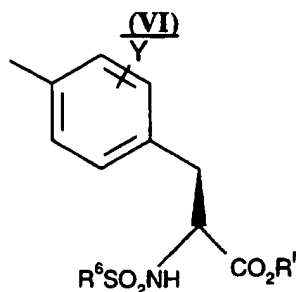
- 20 R²¹ and R²² independently are H or -Z-CO₂R^f or Z-CON(R^f)₂ with the proviso that one of

R²¹ or R²² is -Z-CO₂R^f or Z-CON(R^f)₂;

Z is -CH₂-, -O(CH₂)_q-, -NR^f(CH₂)_q-, -S(CH₂)_q-, -CH₂CH₂-, -CH(CH₃)CH₂-, -(CH₂)₃-, -

CH=CH-, -C(CH₃)=CH-, CH₂-CH=CH- or CH=CHCH₂; and

- 25 Y is H, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, F, Cl, Br, I, CF₃, OR^f, S(O)_kR^f, COR^f, NO₂, N(R^f)₂, CO(NR^f)₂, CH₂N(R^f)₂, methylenedioxy or Z-COR^f, disclosed in Alig, et al., EP 0 381 033, published August 8, 1990.

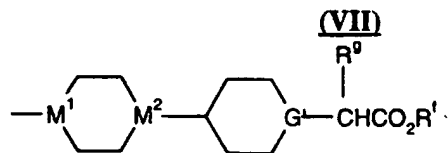


wherein:

- R^6 is aryl, C_{1-10} alkyl, C_{3-6} cycloalkyl, C_{4-10} aralkyl, C_{1-10} alkoxyalkyl, C_{1-10} alkaryl, C_{1-10} alkylthioalkyl, C_{1-10} alkoxythioalkyl, C_{1-10} alkylamino, C_{4-10} aralkylamino, C_{1-10} alkanoylamino, C_{4-10} aralkanoylamino, C_{1-10} alkanoyl, C_{4-10} aralkanoyl, or C_{1-10} carboxyalkyl; and

- Y is H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, F, Cl, Br, I, CF_3 , OR^f , $S(O)_kR^f$, COR^f , NO_2 , $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, CO_2R^f , $OC(O)R^f$, or $NHC(O)R^f$,

disclosed in Egbertson, et al., EP 0 478 328, published April 1, 1992.



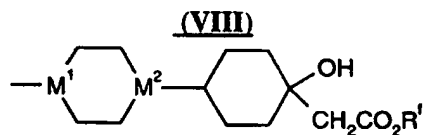
- wherein:

M^1 is CH or N;

M^2 is CH or N, with the proviso that when M^1 is CH, M^2 is N; and

G is N or $N^{\oplus}R''$,

disclosed in Eldred, et al., EP 0542 363, published May 19, 1993.

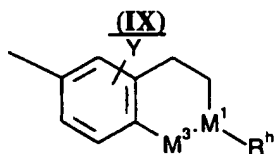


wherein:

M^1 is CH or N; and

M^2 is CH or N, with the proviso that when M^1 is CH, M^2 is N,

- disclosed in Porter, et al., EP 0 537 980, published April 21, 1993.



wherein:

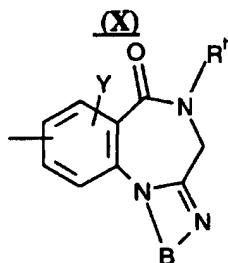
M^1 is CH or N;

- 5 Y is H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, F, Cl, Br, I, CF_3 , OR^f , $S(O)_kR^f$, COR^f , NO_2 , $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, CO_2R^f , $OC(O)R^f$, or $NHC(O)R^f$;

D^3 is CH_2 or $C=O$; and

R^h is $(CH_2)_qCO_2R^f$,

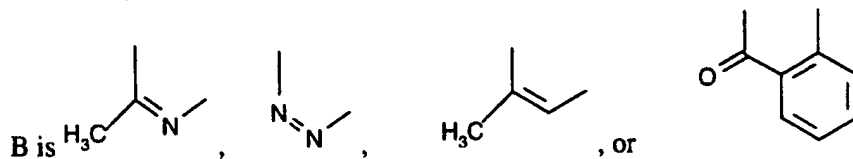
- 10 disclosed in Klinnick, et al., EP 0 635,492, published January 25, 1995.



wherein:

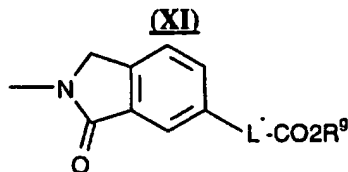
- 15 Y is H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, F, Cl, Br, I, CF_3 , OR^f , $S(O)_kR^f$, COR^f , NO_2 , $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, CO_2R^f , $OC(O)R^f$, or $NHC(O)R^f$;

R^h is $(CH_2)_nCO_2R^f$; and



disclosed in Blackburn, et al., WO 95/04057, published February 9, 1995.

20

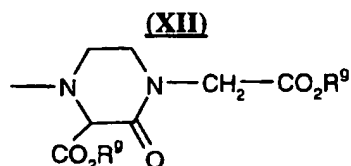


wherein:

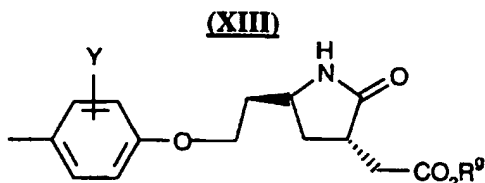
L^* is $-C(O)NR^g-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $NR^g-(CH_2)_q-$, $-O-(CH_2)_q-$, or

- 25 $S(O)_k-(CH_2)_q-$,

disclosed in Hartman, et al., EP 0 540 331, published May 5, 1993.



disclosed in Sugihara, et al., EP 0 529,858, published March 3, 1993.

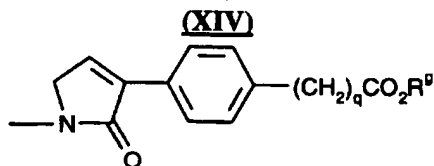


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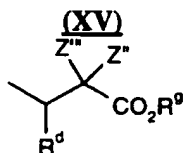
wherein:

Y is H, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, F, Cl, Br, I, CF₃, OR^f, S(O)_kR^f, COR^f, NO₂, N(R^f)₂, CO(NR^f)₂, CH₂N(R^f)₂, methylenedioxy, CN, CO₂R^f, OC(O)R^f, or NHC(O)R^f,

10 disclosed in Himmeisbach, et al., EP 0 483 667, published May 6, 1992.



disclosed in Linz, et al., EP 0 567 968, published November 3, 1993.



15

wherein:

R^d is Het-C₀₋₆alkyl; and

Z'', Z''' independently are hydrogen, C₁₋₄alkyl, halo, OR^f, CN, S(O)_kR^f, CO₂R^f, or OH,

20 disclosed in Bovy, et al., EP 0 539 343, published April 28, 1993.

The above descriptions of fibrinogen receptor templates for use in the present invention were taken from pending published patent applications. Reference should be made to such patent applications for their full disclosures, including the variations possible for such templates and methods of preparing said templates, the entire disclosure of such patent applications being incorporated herein by reference.

25

In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E)

isomers are within the scope of this invention. The meaning of any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of this invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984).

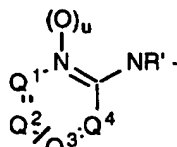
C₁₋₄alkyl as applied herein means an optionally substituted alkyl group of 1 to 4 carbon atoms, and includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. C₁₋₆alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C₀₋₄alkyl and C₀₋₆alkyl additionally indicates that no alkyl group need be present (*e.g.*, that a covalent bond is present).

Any C₁₋₄alkyl or C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl or C₁₋₆ oxoalkyl may be optionally substituted with the group R^x, which may be on any carbon atom that results in a stable structure and is available by conventional synthetic techniques. Suitable groups for R^x are C₁₋₄alkyl, OR', SR', C₁₋₄alkyl, C₁₋₄alkylsulfonyl, C₁₋₄alkylsulfoxyl, -CN, N(R')₂, CH₂N(R')₂, -NO₂, -CF₃, -CO₂ R', -CON(R')₂, -CO R', -N R'C(O) R', OH, F, Cl, Br, I, N₃ or CF₃S(O)_r-, wherein r is 0 to 2 and R' is as defined with respect to formula (II).

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to three substituents, such as those defined above for alkyl, especially C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkthio, CO₂H, N₃, trifluoroalkyl, OH, F, Cl, Br or I.

Het, or heterocycle, indicates an optionally substituted five or six membered monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable and available by conventional chemical synthesis. Illustrative heterocycles are benzofuryl, benzimidazole, benzopyran, benzothiophene, biotin, furan, imidazole, indoline, morpholine, piperidine, piperazine, pyrrole, pyrrolidine, tetrahydropyridine, pyridine, thiazole, thiophene, quinoline, isoquinoline, and tetra- and perhydro- quinoline and isoquinoline. Any accessible combination of up to three substituents on the Het ring, such as those defined above for alkyl that are available by chemical synthesis and are stable are within the scope of this invention.

C₃₋₇cycloalkyl refers to an optionally substituted carbocyclic system of three to seven carbon atoms, which may contain up to two unsaturated carbon-carbon bonds. Typical of C₃₋₇cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl and cycloheptyl. Any combination of up to three substituents, such as those defined above for alkyl, on the cycloalkyl ring that is available by conventional chemical synthesis and is stable, is within the scope of this invention.

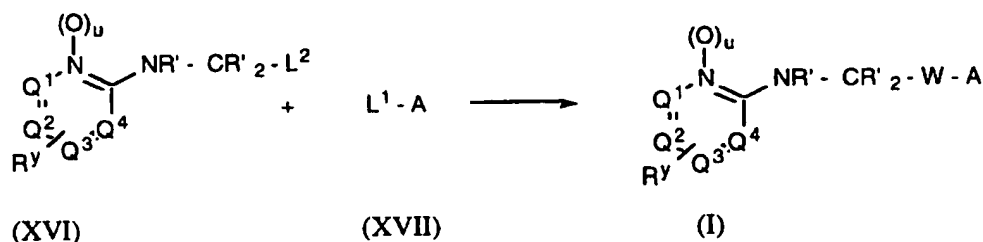


The ring represented by R^Y is a six-membered ring containing at least one nitrogen which is substituted in the 2 position with a nitrogen atom. The ring may optionally have an additional nitrogen atom in the ring, and hence may be a pyrazine, pyridazine or a pyrimidine. The substituent R^Y may be in any position on $Q^1 - Q^4$ which results in a stable structure. It will be apparent that when the value of u is 1 the compound described will be an N-oxide; whereas, when the value of u is 0 there is no oxygen substituent on the nitrogen. A pyridine ring is preferred.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical, BrZ refers to the o-bromobenzyloxycarbonyl radical, ClZ refers to the o-chlorobenzyloxycarbonyl radical, Bzl refers to the benzyl radical, 4-MBzl refers to the 4-methyl benzyl radical, Me refers to methyl, Et refers to ethyl, Ac refers to acetyl, Alk refers to C_{1-4} alkyl, Nph refers to 1- or 2-naphthyl and cHex refers to cyclohexyl. Tet refers to 5-tetrazolyl.

Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethyl amine, EDC refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride. HOBT refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DME refers to dimethoxyethane, DMF refers to dimethylformamide, NBS refers to N-bromosuccinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to 1-propanephosphonic acid cyclic anhydride, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

Compounds of the formula (I) are generally prepared by reacting a compound of formula (XVI) with a compound of formula (XVII), wherein L^1 and L^2 are groups which may react to form a covalent bond in the moiety W, by methods generally known in the art.



Typical methods include coupling to form amide bonds, nucleophilic displacement reactions and palladium catalyzed couplings.

5 For instance, when W contains an ether or amine linkage, the bond may be formed by a displacement reaction, and one of L¹ and L² will contain an amino or hydroxy group and the other will contain a displaceable group, such as a chloro, bromo or iodo group. When W contains an amide bond, typically one of L¹ and L² will contain an amino group, and the other will contain a carboxylic acid group. In another approach, L¹ may be an
 10 aryl or heteroaryl bromide, iodide or trifluoromethylsulfonyloxy derivative and L² may contain an amino group and the amide linkage may be formed by palladium-catalyzed aminocarbonylation with carbon monoxide in a suitable solvent such as dimethylformamide or toluene.

It will be apparent that the precise identity of L¹ and L² will be dependent upon
 15 the site of the linkage being formed. General methods for preparing the linkage - (CHR'')_r-U-(CHR')_s-V- are described, for example, in EP-A 0 372 486 and EP-A 0 381 033 and EP-A 0 478 363, which are incorporated herein by reference.

For instance, if V is CONH, L¹ may be -NH₂, L² may be OH (as in an acid) or Cl (as in an acid chloride). For instance, (pyrid-2-yl) aminomethyl(CH₂)_a-COCl may be
 20 reacted with a suitable amine. When L² is OH, a coupling agent is used.

Similarly, if V is NHCO, L¹ may be -CO₂H or CO-Cl, L² may be -NH₂. For instance, (pyrid-2-yl)aminomethyl(CH₂)_a-NHR' may be reacted with a suitable carboxylic acid.

Where V is NHSO₂, L¹ may be SO₂Cl, L² may be -NH₂ as above. Where V is
 25 SO₂NH, L¹ may be -NH₂ and L² may be SO₂Cl. Methods to prepare such sulfonyl chlorides are disclosed, for instance, in *J. Org. Chem.*, 23, 1257 (1958).

If V is CH=CH, L¹ may be -CHO, L² may be CH=P-Ph₃. Alternately, L¹ may be CH=P-Ph₃ and L² may be CHO. For instance, (pyrid-2-yl)aminomethyl (CH₂)_a-CHO may be reacted with a suitable phosphorane.

Where V is CH₂CH₂ may be obtained by reduction of a suitably protected
5 compound wherein V is CH=CH.

Where V is CH₂O, CH₂N or C≡C, L¹ may be -OH, -NH or -C≡CH, respectively; L² may be -Br or -I. Similarly where U or V is OCH₂, NR'¹CH₂ or C≡C, L¹ may be -CH₂Br and L² may be -OH, -NH or -C≡CH, respectively. For example, (pyrid-2-yl)aminomethyl(CH₂)_a-Br may be reacted with an appropriate amine, alkoxide or
10 acetylene. Alternately, when U or V is C≡C, L¹ may be Br, I or CF₃SO₃, L² may be C≡CH and the coupling may be catalyzed by palladium and a base.

Compounds wherein V is CHOHCH₂ may be prepared from a suitably protected compound where V is CH=CH by the procedure disclosed in *J. Org. Chem.*, 54, 1354 (1989).

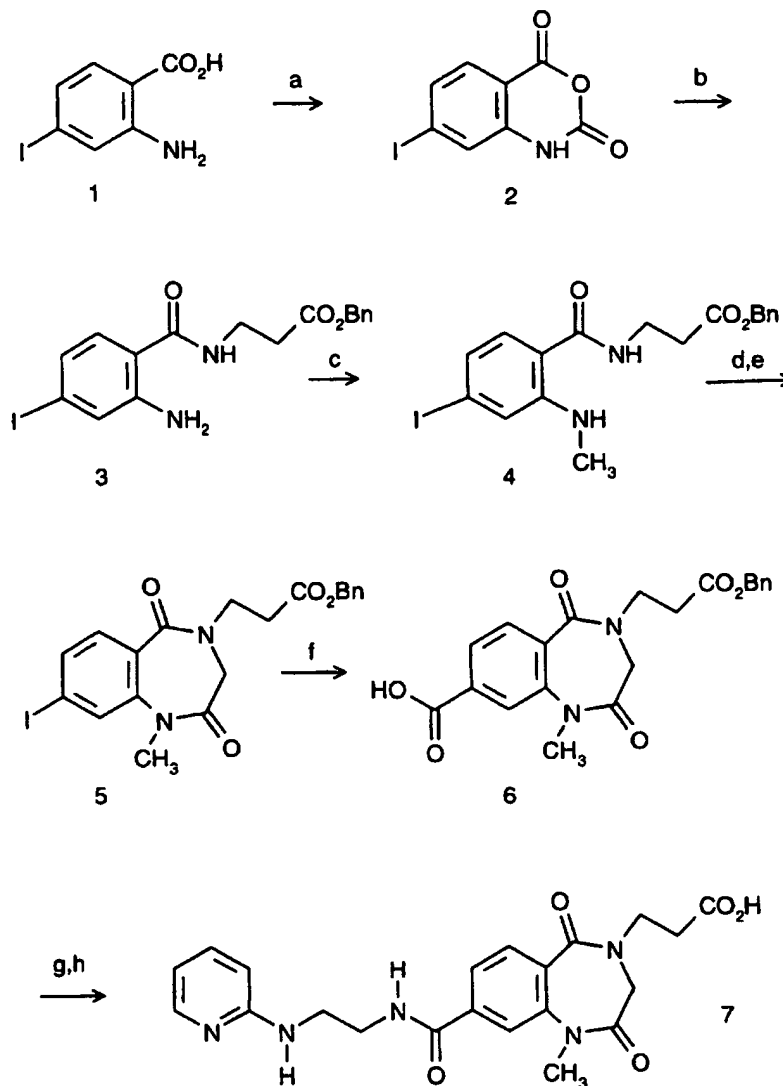
15 Compounds wherein V is CH₂CHOH may be obtained from a suitably protected compound where V is CH=CH by hydroboration and basic oxidation as disclosed in *Tet. Lett.*, 31, 231 (1990).

The core 6-7 fused ring fibrinogen template of formula (II) is prepared by methods well known in the art, *e.g.*, Hynes, *et al.*, *J. Het. Chem.*, 1988, 25, 1173; Muller, *et al.*,
20 *Helv. Chim. Acta.*, 1982, 65, 2118; Mori, *et al.*, *Heterocycles*, 1981, 16, 1491. Similarly, methods for preparing benzazepines, 1,4-benzothiazepines, 1,4-benzoxazepines and 1,4-benzodiazepines are known and are disclosed, for instance, in Bondinell, *et al.*, International Patent Application WO 93/00095.

Representative fibrinogen antagonist templates may be prepared according to
25 Schemes A - CC, which follow:

Scheme A describes a method of preparing exemplary fibrinogen receptor templates described in Blackburn, *et. al.*, WO 93/08174.

Scheme A



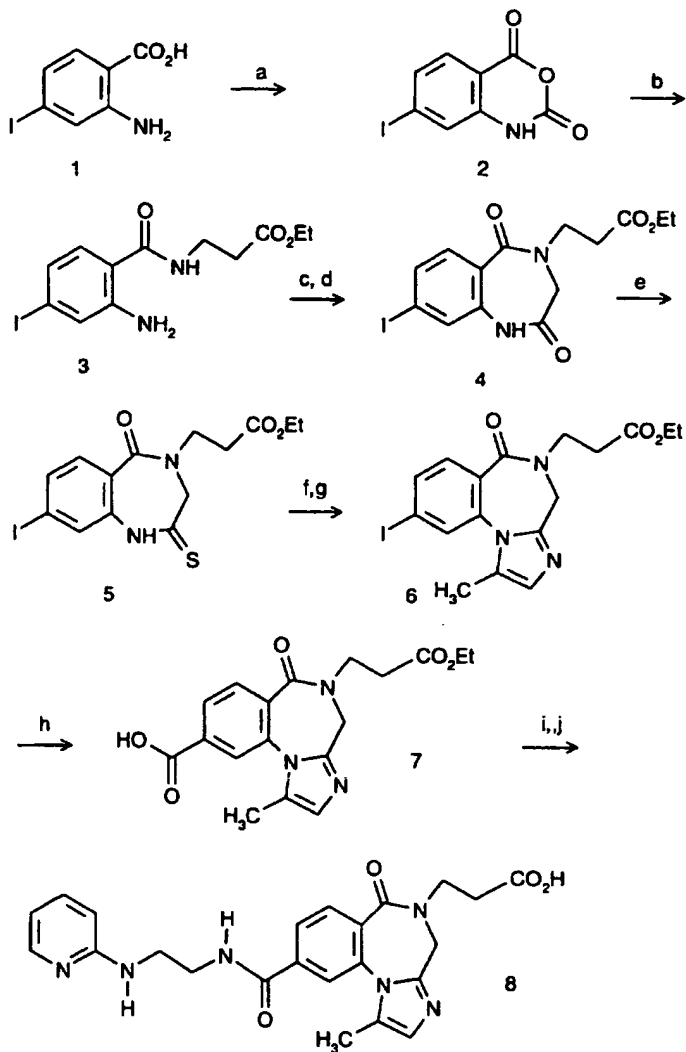
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- a) COCl_2 , Na_2CO_3 , toluene; b) β -alanine benzyl ester tosylate, DMAP, pyridine; c) CH_3I , 2,6-lutidine, DMF; d) α -bromoacetyl bromide, Et_3N , CH_2Cl_2 ; e) NaH , DMF, f) $\text{Pd}(\text{OAc})_2$, dppf, CO , DMSO, 65°C , 18 h; g) N-(2-pyridinyl)ethylenediamine, EDC, HOBT· H_2O , DIEA, CH_3CN ; h) H_2 , 10% Pd/C , EtOH .

10

Scheme B describes a method of preparing exemplary fibrinogen receptor templates described in Blackburn, *et. al.*, WO 95/04057.

Scheme B



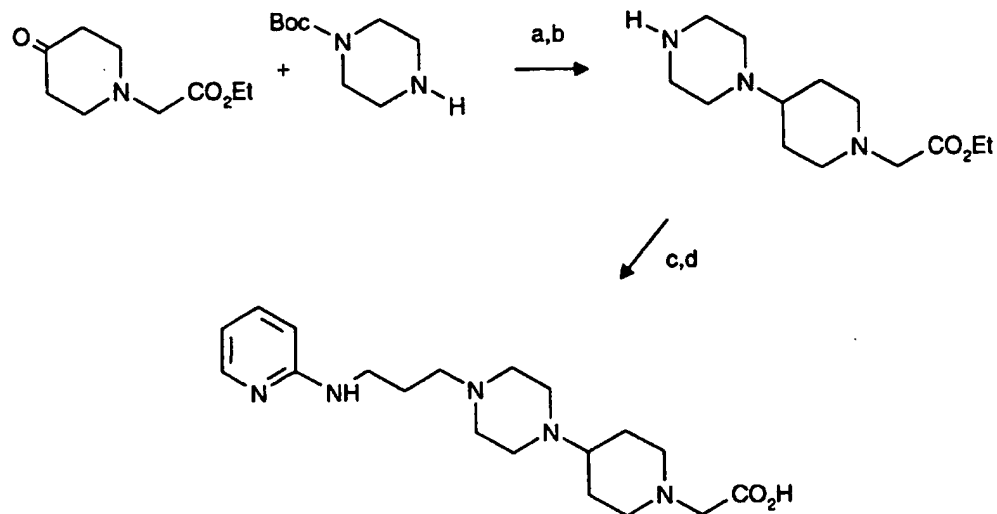
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- a) COCl₂, NaHCO₃, toluene; b) β-alanine ethyl ester hydrochloride, DMAP, pyridine; c) α-bromoacetyl bromide, Et₃N, CH₂Cl₂; d) NaH, DMF; e) Lawesson's reagent, THF, 50°C, 2 h; f) CH₃I, NaOH, (n-Bu)₄N.HSO₄, CH₂Cl₂/H₂O, RT, 2 h; g) propargyl amine, toluene, pyridine hydrochloride, reflux, 6 h; h) Pd(OAc)₂, dppf, CO, DMSO, 65°C, 18 h; i) N-(2-pyridinyl)ethylenediamine, EDC, HOBT·H₂O, DIEA, CH₃CN; j) LiOH, H₂O, THF, 18 h.

10

Scheme C describes a method of preparing exemplary fibrinogen receptor templates described in Porter, *et al.*, EP 0542363.

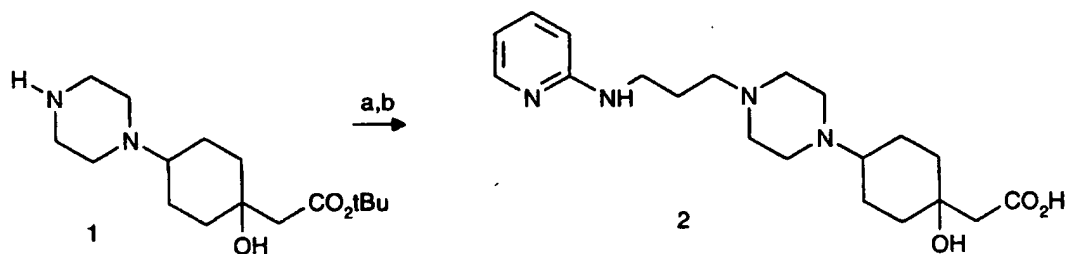
Scheme C



a) NaBH_3CN , HCl , CH_3OH ; b) HCl , dioxane, CH_2Cl_2 ; c) 1-chloro-3-[(2-pyridinyl)amino]propane, DIEA, THF; d) NaOH , H_2O , CH_3OH .

10 Scheme D describes a method of preparing exemplary fibrinogen receptor
templates described in Porter, *et al.*, EP 0537980.

Scheme D

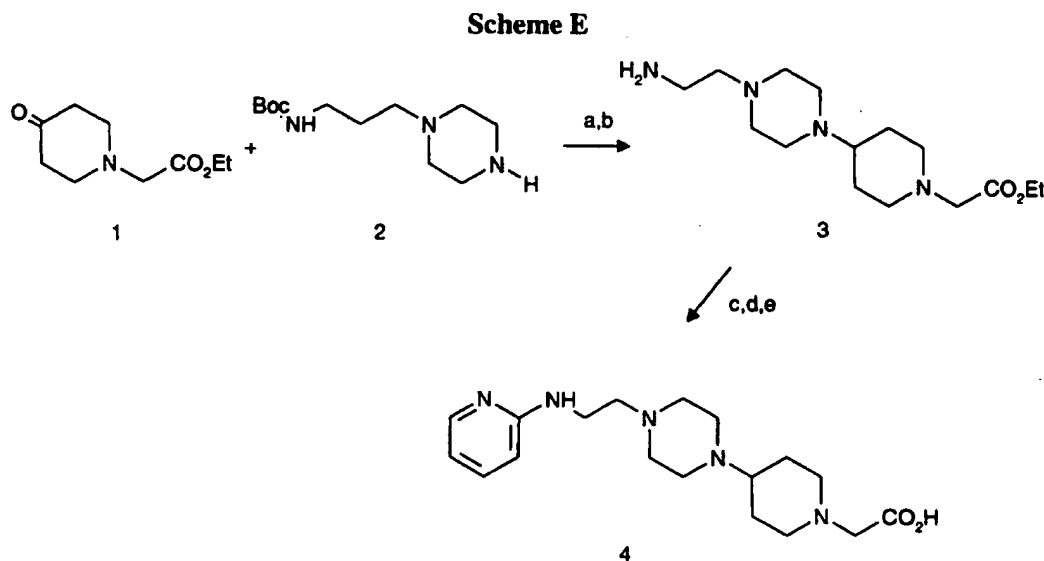


a) 1-chloro-3-[(2-pyridinyl)amino]propane, DIEA, THF; b) NaOH, H₂O, CH₃OH.

D-1 is alkylated with 1-chloro-3-[(2-pyridinyl)amino]propane with DIEA in THF, the resulting ester is saponified with NaOH in aqueous CH₃OH to give **D-2**.

Alternatively, the tert-butyl ester can be cleaved with TFA or HCl in a suitable solvent such as CH₂Cl₂ or dioxane.

- 5 Scheme E describes a method of preparing exemplary fibrinogen receptor templates described in Porter, *et al.*, EP 0542363.

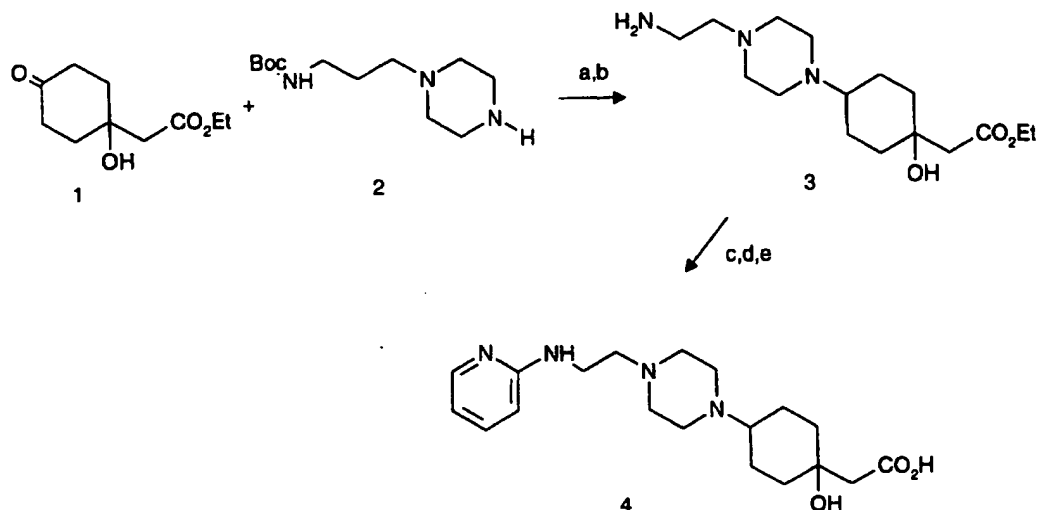


- 10 a) NaBH₃CN, HCl, CH₃OH, EtOH, molecular sieves; b) TFA, CH₂Cl₂; c) 2-chloropyridine-N-oxide, NaHCO₃, butanol; d) HCO₂K, 10% Pd/C, CH₃OH; e) 1N NaOH, CH₃OH.

- 15 Reductive amination of **E-1** with **E-2** using NaBH₃CN, HCl, and molecular sieves in CH₃OH and EtOH, followed by treatment of the product with TFA in CH₂Cl₂ gives **E-3**. Treatment of **E-3** with 2-chloropyridine-N-oxide and NaHCO₃ in butanol with heating, followed by reduction of the N-oxide with HCO₂K and 10% Pd/C in CH₃OH, and saponification of the ethyl ester with 1N NaOH in CH₃OH gives **E-4**.

Scheme F describes a method of preparing exemplary fibrinogen receptor templates described in Porter, *et al.*, EP 0537980.

Scheme F



a) NaBH_3CN , HCl , CH_3OH , EtOH , molecular sieves; b) TFA , CH_2Cl_2 ; c) 2-chloropyridine-*N*-oxide, NaHCO_3 , butanol; d) HCO_2K , 10% Pd/C , CH_3OH ; e) 1N NaOH , CH_3OH .

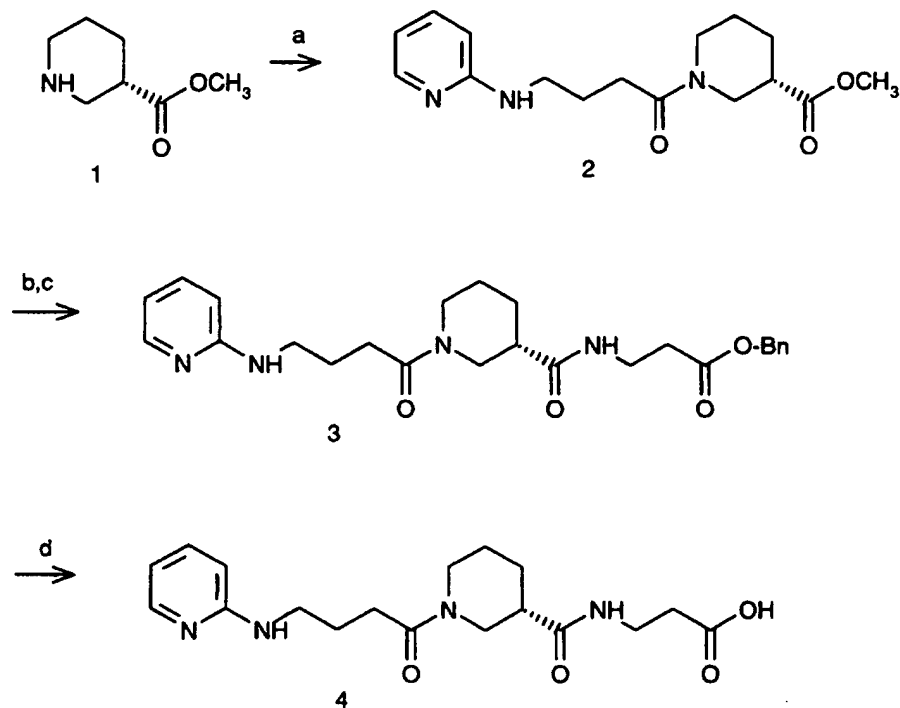
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Reductive amination of **F-1** with **F-2** using NaBH_3CN , HCl , and molecular sieves in CH_3OH and EtOH , followed by treatment of the product with TFA in CH_2Cl_2 gives **F-3**. Treatment of **E-3** with 2-chloropyridine-*N*-oxide and NaHCO_3 in butanol with heating, followed by reduction of the *N*-oxide with HCO_2K and 10% Pd/C in CH_3OH , and saponification of the ethyl ester with 1*N* NaOH in CH_3OH gives **F-4**.

15

Scheme G describes a method of preparing exemplary fibrinogen receptor templates described in Beavers, *et al.*, WO 95/25091.

Scheme G



5

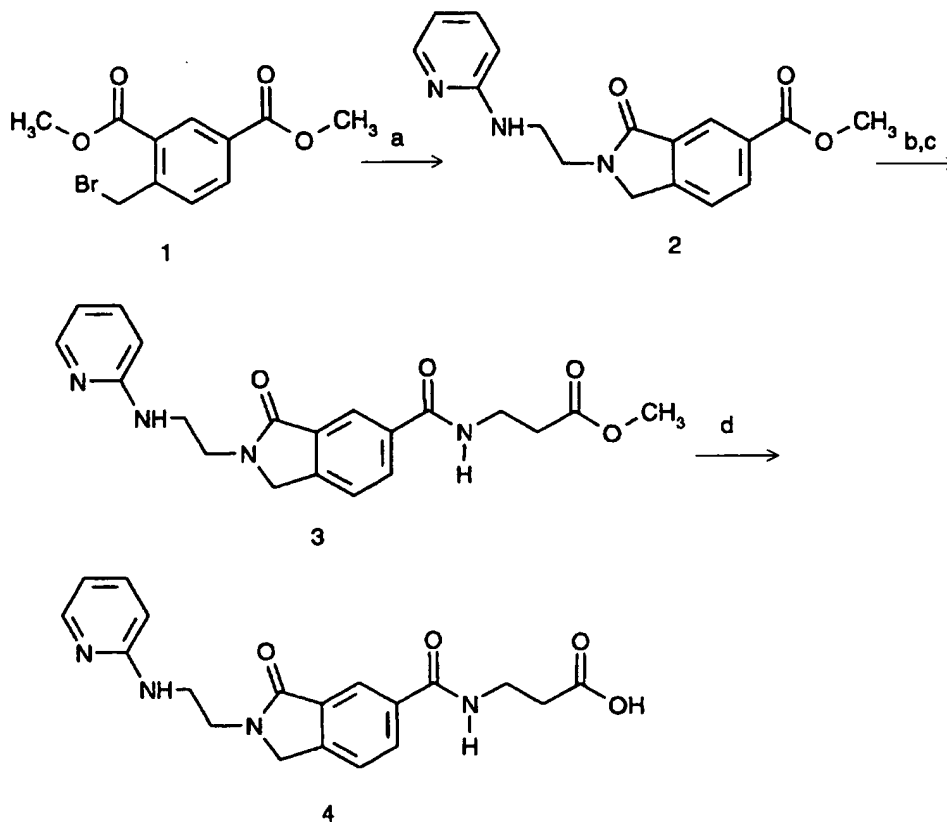
a) N-[2-(pyridinyl)amino]butyric acid, BOP-Cl, NMM, CH₂Cl₂; b) LiOH, H₂O, THF; c) β -alanine benzyl ester, EDC, HOBT, NMM, CH₂Cl₂; d) H₂, 10% Pd/C, AcOH, THF, H₂O.

10

Following the procedures of Beavers, *et al.*, WO 95/25091, Example 1, except substituting N-[2-(pyridinyl)amino]butyric acid, for N ^{α} -Boc-D-lys(Cbz)-OH, gives **F-4**.

Scheme H describes a method of preparing exemplary fibrinogen receptor templates described in Hartman, *et al.*, EP 0540334.

Scheme H

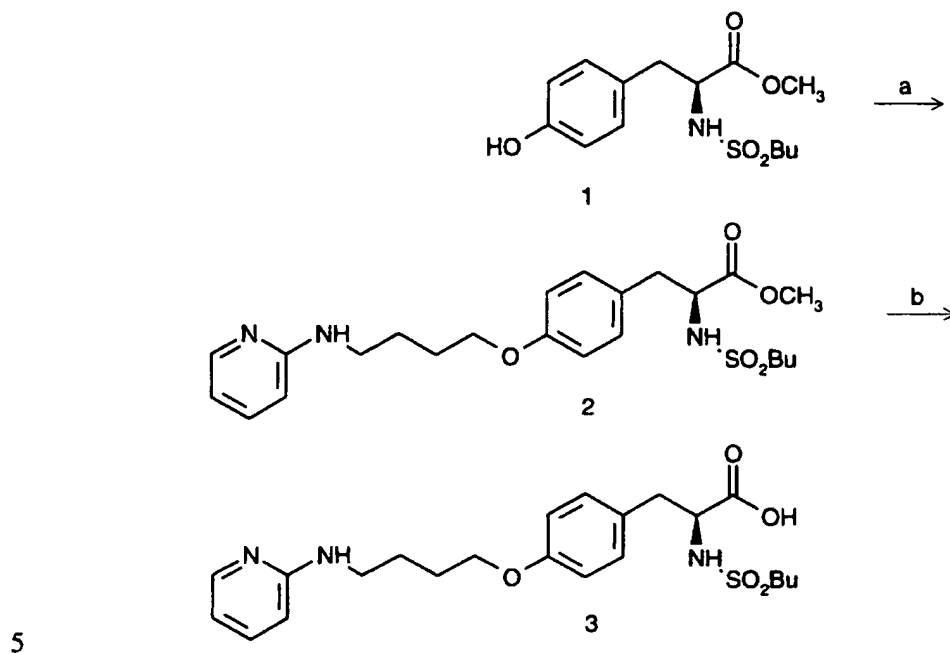


a) N-(2-pyridinyl)ethylenediamine, Et₃N, benzene; b) 1.0 N LiOH, H₂O, CH₃OH; c) β -alanine ethyl ester, BOP, Et₃N, CH₃CN; d) LiOH, H₂O, THF, CH₃OH.

- 10 Dimethyl 4-(bromomethyl)benzene-1,3-dicarboxylate, **H-1**, is treated with a suitably functionalized amine, such as N-(2-pyridinyl)ethylenediamine, under the general conditions described for 2,3-dihydro-N-(2-carboxy-ethyl)-2-[2-(piperidinyl)ethyl]-3-oxo-1H-isoindole-5-carboxamide in Hartman, *et al.*, EP 0540334, to give **H-4**.

Scheme I describes a method of preparing exemplary fibrinogen receptor templates described in Egbertson, *et al.*, EP 0478363.

Scheme I

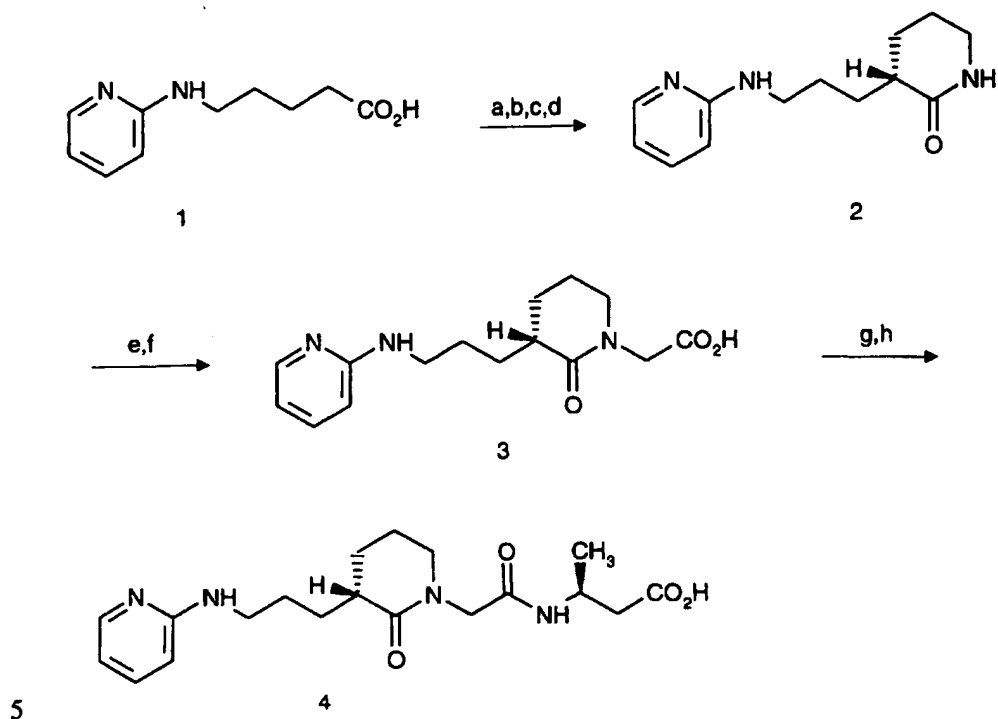


a) 4-[(2-pyridinyl)amino]butanol, Ph_3P , DEAD, CH_2Cl_2 , benzene; b) 1.0 N LiOH, THF, H_2O .

10 N-(n-Butylsulfonyl)-L-tyrosine methyl ester, **I-1**, is treated with a suitably functionalized alcohol, such as 4-[(2-pyridinyl)amino]butanol, to give **I-3**.

Scheme J describes a method of preparing exemplary fibrinogen receptor templates described in Duggan, *et al.*, *J. Med. Chem.* **1995**, 38, 3332.

Scheme J



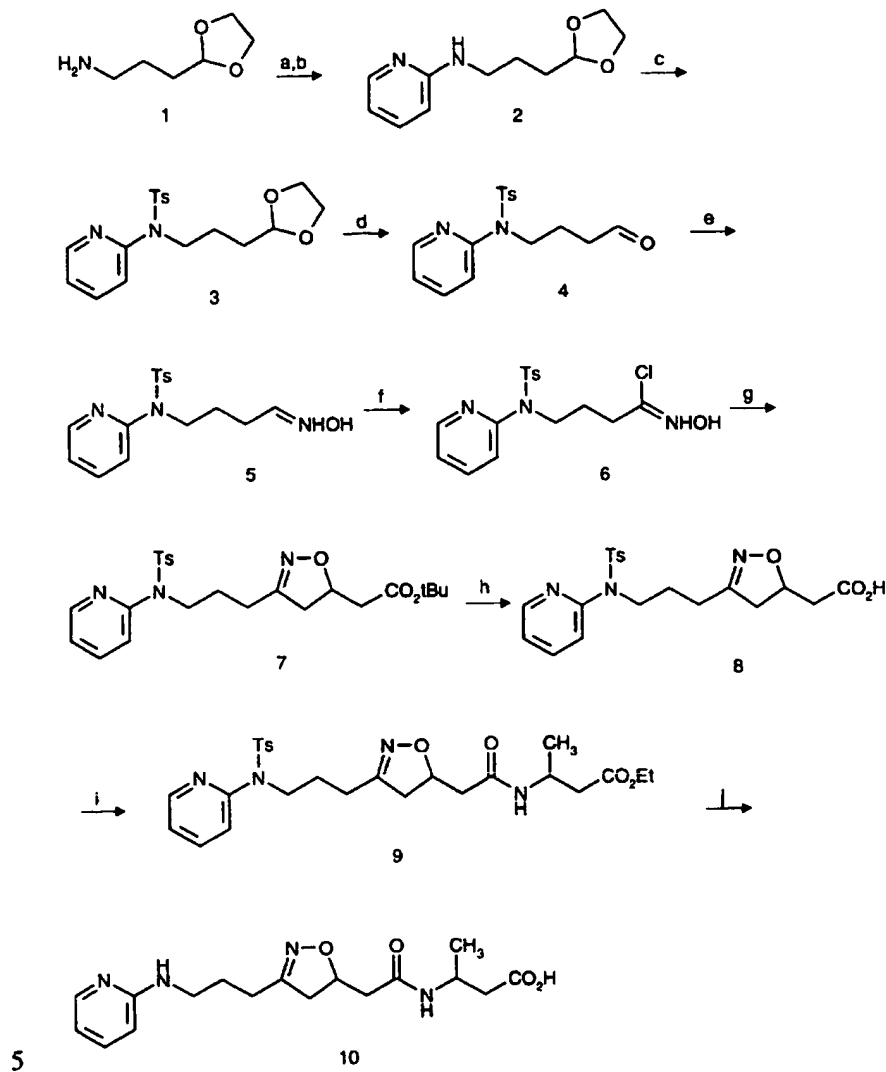
- a) pivaloyl chloride, Et₃N, THF, (S)-4-benzyl-2-oxazolidinone; b) Ti(O-*i*-Pr)Cl₂, acrylonitrile, DIEA, CH₂Cl₂; c) H₂, PtO₂, CH₃OH, CHCl₃; d) NaHCO₃, CH₃CN; e) NaHMDS, ethyl bromoacetate; f) 1 N NaOH, CH₃OH; g) 3(R)-methyl-β-alanine ethyl ester HCl, EDC, HOBT, Et₃N, DMF; h) 1 N NaOH, CH₃OH.

A suitably functionalized carboxylic acid, such as 5-[(pyrid-2-yl)amino]pentanoic acid, **J-1**, is activated and reacted with a chiral auxiliary such as lithium (S)-4-benzyl-2-oxazolidinone to form a chiral Evans reagent. Alkylation of the titanium enolate with acrylonitrile, followed by nitrile reduction and lactam formation affords lactam **J-2**. Alkylation of the lactam with agents such as ethyl bromoacetate followed by ester saponification yields the carboxylic acid **J-3**. The resulting carboxylic acid derivative **J-3** is converted to an activated form of the carboxylic acid using, for example, EDC and HOBT, or SOCl₂, and the activated form is subsequently reacted with an appropriate

amine, for instance the 3(R)-methyl- β -alanine ethyl ester, in a suitable solvent such as DMF, CH_2Cl_2 , or CH_3CN . Depending on whether acid neutralization is required, an added base, such as DIEA or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Hydrolysis of the ethyl ester is accomplished according to the general conditions described for the conversion of J-2 to J-3, to provide the carboxylic acid J-4. Alternatively, the intermediate carboxylate salt of can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

Scheme K describes a method of preparing exemplary fibrinogen receptor templates described in WO 93/07867.

Scheme K



- a) 2-chloropyridine N-oxide hydrochloride, NaHCO_3 , tert-amyl alcohol; b) HCO_2NH_4 , Pd/C , EtOH ; c) TsCl , NaH , THF ; d) $p\text{-TsOH}\cdot\text{H}_2\text{O}$, acetone, H_2O ; e) $\text{NH}_2\text{OH}\cdot\text{HCl}$, NaOAc , CH_3OH ; f) NCS , DMF ; g) tert-butyl 3-butenolate, Et_3N ; h) 4M HCl , dioxane, CH_2Cl_2 ; i) ethyl 3-aminobutyrate, EDC , $\text{HOBT}\cdot\text{H}_2\text{O}$, DIEA , CH_3CN ; j) 1.0 N LiOH , THF , H_2O .

Readily available 2-(3-aminopropyl)-1,3-dioxolane, **K-1**, *Chem. Pharm. Bull.* **1982**, *30*, 909-914, is converted to the pyridyl derivative **K-2** according to the general protocol described by Misra, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2165-2170. Protection of one of the nitrogen atoms of the aminopyridine moiety in **K-2** can be accomplished by

5 reaction with a sulfonyl chloride, for instance p-toluenesulfonyl chloride, in the presence of a suitable base, generally NaH or an aqueous alkali metal hydroxide, in an inert solvent, preferably THF, to afford **K-3**. Alternative protecting groups known to those of skill in the art may be used, as long as they are compatible with the subsequent chemistry and can be removed when desired. Such protecting groups are described in Greene,

10 "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Removal of the dioxolanyl protecting group of **K-3** to afford the aldehyde **K-4** can be conveniently accomplished under mild acidic conditions, such as p-toluenesulfonic acid, in an appropriate solvent, preferably aqueous acetone. The aldehyde is converted to the aldoxime **K-5** by standard procedures known to those of skill in the art, and this aldoxime

15 is oxidized to the oximinoyl chloride derivative **K-6** by the methods described in WO 95/14682 and WO 95/14683. Reaction of **K-6** with an olefin, such as tert-butyl 3-butenate (*Tet. Lett.* **1985**, *26*, 381-384), in the presence of a suitable base, for instance Et₃N or DIEA, in an inert solvent such as benzene or toluene, according to the protocol described in WO 95/14682 and WO 95/14683, gives the cycloadduct **K-7**. The tert-butyl

20 ester of **K-7** is removed under standard acidic conditions, generally TFA in CH₂Cl₂ or HCl in dioxane, to give the carboxylic acid **K-8**. The carboxylic acid is activated using, for example, EDC and HOBt, or SOCl₂, and the activated form is subsequently reacted with an appropriate amine, for instance a suitable derivative of β-alanine, in a neutral solvent, such as DMF, CH₂Cl₂, or CH₃CN, to afford **K-9**. Depending on whether acid

25 neutralization is required, an added base, such as DIEA or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Derivatives of β-alanine are readily available

30 in either racemic or optically pure form by a variety of methods known to those of skill in

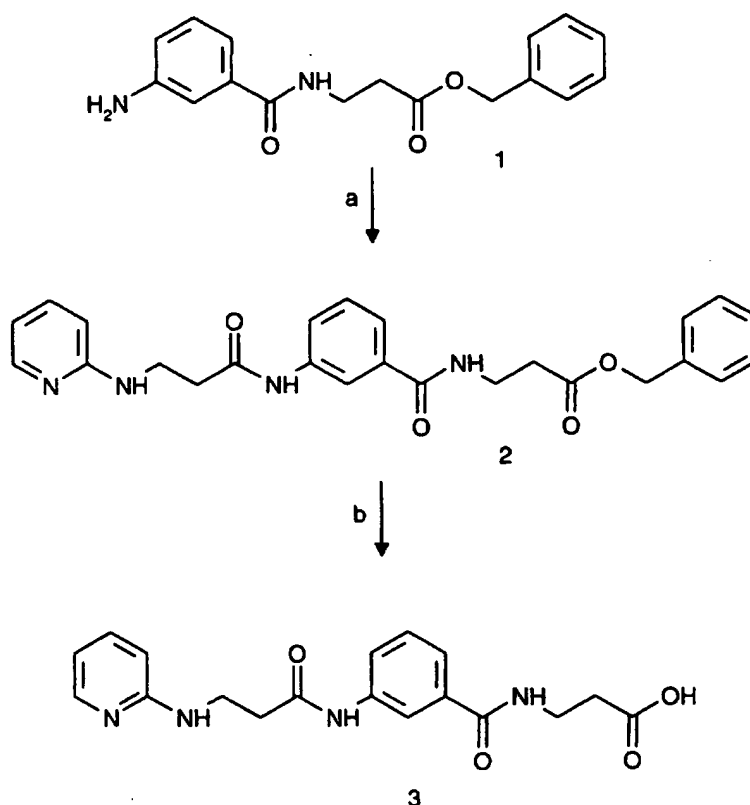
the art. A representative method is described in WO 93/07867. The ethyl ester and sulfonyl protecting groups of **K-9** are removed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous CH₃OH or EtOH. The intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **K-**

- 5 10. Alternatively, the intermediate carboxylate salt can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

Scheme L describes a method of preparing exemplary fibrinogen receptor templates described in Alig, *et al.*, EP 0372486.

10

Scheme L



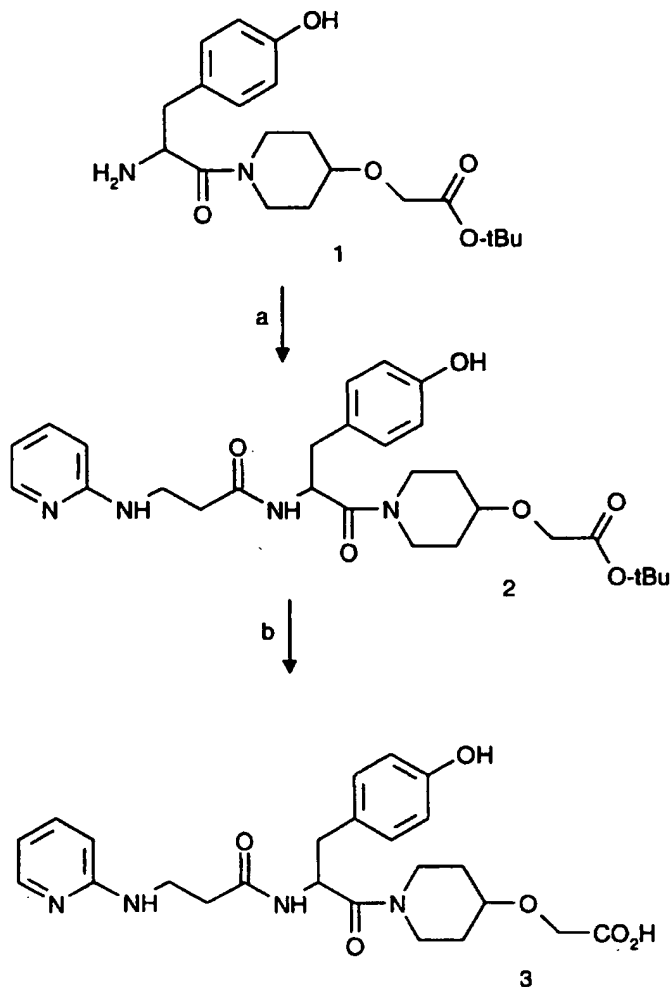
a) N-(2-pyridinyl)-β-alanine, EDC, DIEA, DMF; b) NaOH, H₂O, CH₃OH.

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L-1, prepared as described in Alig *et al.*, EP 0372486, is condensed with a suitable substituted carboxylic acid, such as N-(2-pyridinyl)- β -alanine, in the presence of EDC and DIEA, and in a suitable solvent, e.g., DMF or CH₃CN, to give L-2. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in
5 standard reference books, such as "Compendium of Organic Synthesis", Vol. I-VI (published by Springer-Verlag). Hydrolysis of the ester in L-2 is accomplished by saponification with a suitable reagent, e.g., NaOH, in a suitable solvent, e.g., aqueous CH₃OH. Alternatively, the benzyl ester in L-2 may be converted to the acid by treatment with hydrogen and a suitable catalyst, e.g., Pd/C, in a suitable solvent, e.g., CH₃OH,
10 EtOH, or AcOH.

Scheme M describes a method of preparing exemplary fibrinogen receptor templates described in Alig, *et al.*, EP 0505868.

Scheme M

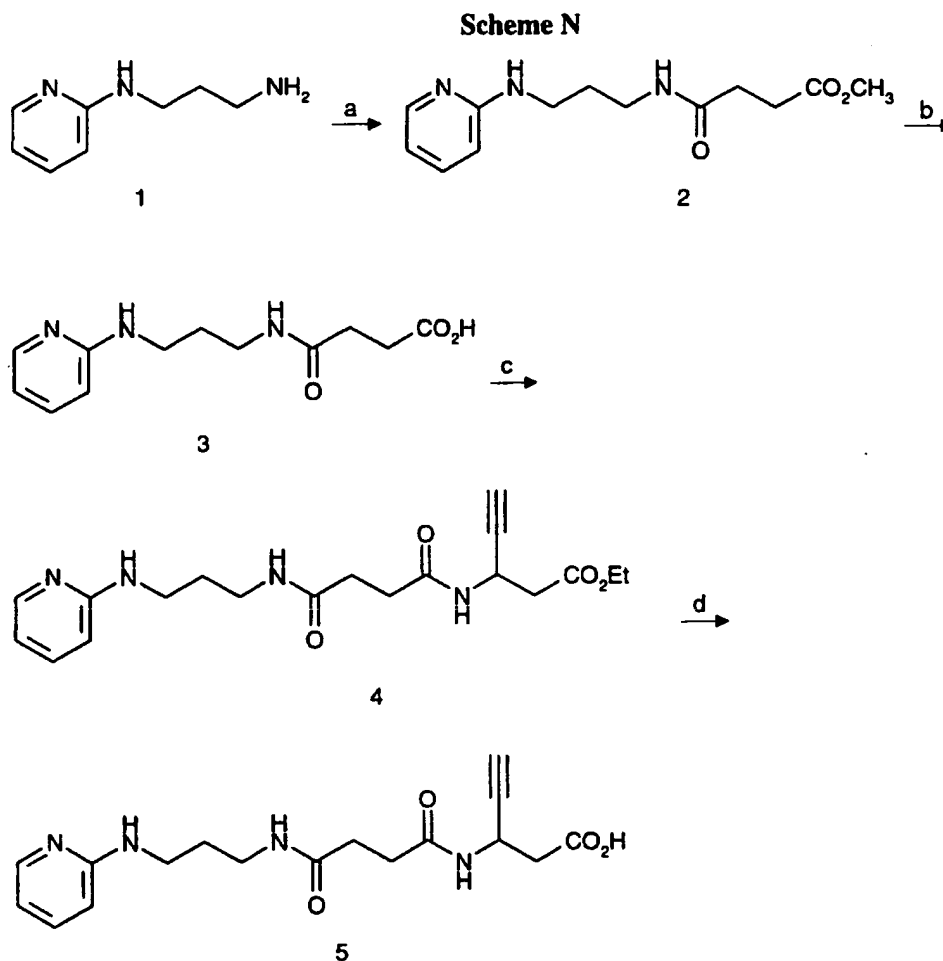


a) N-(2-pyridinyl)-β-alanine, EDC, DIEA, DMF; b) CF₃CO₂H, CH₂Cl₂.

M-1, prepared as described in Alig *et al.*, EP 0505868, is condensed with a suitable substituted carboxylic acid, such as N-(2-pyridinyl)-β-alanine, in the presence of EDC and DIEA, in a suitable solvent, e.g., DMF or CH₃CN, to give **M-2**. Many additional methods for converting a carboxylic acid to an amide are known, and can be

found in standard reference books, such as "Compendium of Organic Synthesis", Vol. I-VI (published by Springer-Verlag). Hydrolysis of the ester in **M-2** is accomplished with trifluoroacetic acid or hydrogen chloride to give **M-3**. Alternatively, the ester in **M-2** may be saponified with a suitable reagent, e.g., 1N NaOH, in a suitable solvent, e.g., CH₃OH.

- 5 Scheme N describes a method of preparing exemplary fibrinogen receptor templates described in WO 93/07867.

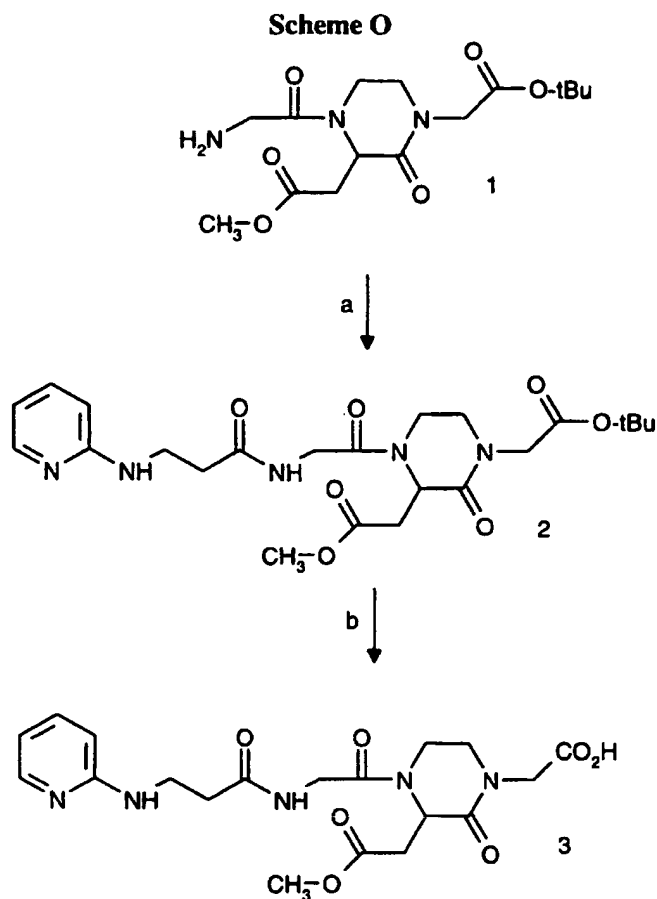


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a) 3-(carbomethoxy)propionyl chloride, DIEA, CH₂Cl₂; b) 1.0 N NaOH, CH₃OH; c) ethyl 3-amino-4-pentynoate, EDC, HOBt·H₂O, DIEA, CH₃CN; d) 1.0 N LiOH, THF, H₂O.

A suitably functionalized amine, such as 2-[(3-aminoprop-1-yl)amino]pyridine, is reacted with 3-(carbomethoxy)propionyl chloride in the presence of an appropriate acid scavenger, such as Et₃N, DIEA, or pyridine, in a neutral solvent, generally CH₂Cl₂, to afford N-2. The methyl ester of N-2 is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous CH₃OH or EtOH, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid N-3. Alternatively, N-1 can be reacted with succinic anhydride in the presence of an appropriate base, such as Et₃N, DIEA, or pyridine, in a neutral solvent, generally CH₂Cl₂, to afford N-3 directly. The resulting carboxylic acid derivative N-3 is converted to an activated form of the carboxylic acid using, for example, EDC and HOBT, or SOCl₂, and the activated form is subsequently reacted with an appropriate amine, for instance the known ethyl 3-amino-4-pentynoate (WO 93/07867), in a suitable solvent such as DMF, CH₂Cl₂, or CH₃CN, to N-4. Depending on whether acid neutralization is required, an added base, such as DIEA or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Hydrolysis of the ethyl ester of N-4 is accomplished according to the general conditions described for the conversion of N-2 to N-3, to provide the carboxylic acid N-5. Alternatively, the intermediate carboxylate salt of can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

Scheme O describes a method of preparing exemplary fibrinogen receptor templates described in Sugihara, *et al.*, EP 0529858.

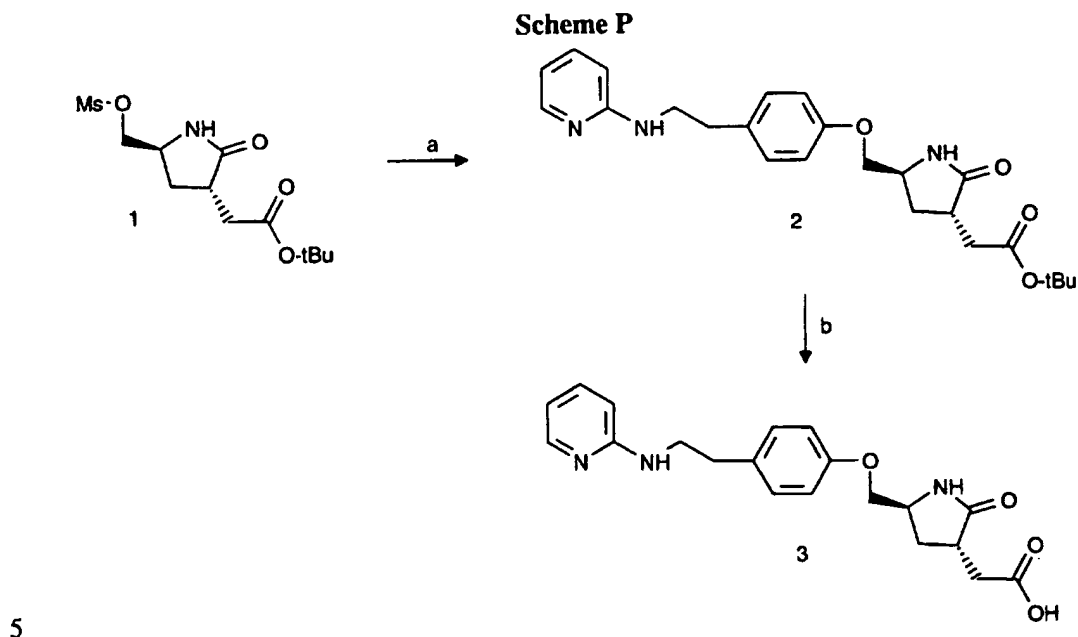


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a) N-(2-pyridinyl)-β-alanine, EDC, DIEA, DMF; b) CF₃CO₂H, CH₂Cl₂.

O-1, prepared as described in Sugihara, *et al.*, EP 0529858, is condensed with a suitable substituted carboxylic acid, such as N-(2-pyridinyl)-β-alanine, to give **O-2**, and the tert-butyl ester is cleaved with TFA, following the general procedure of Sugihara, *et al.*, Example 59, to give **O-3**. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthesis", Vol. I-VI (published by Springer-Verlag).

Scheme P describes a method of preparing exemplary fibrinogen receptor templates described in Himmelsbach, *et al.*, AU-A-86926/91.

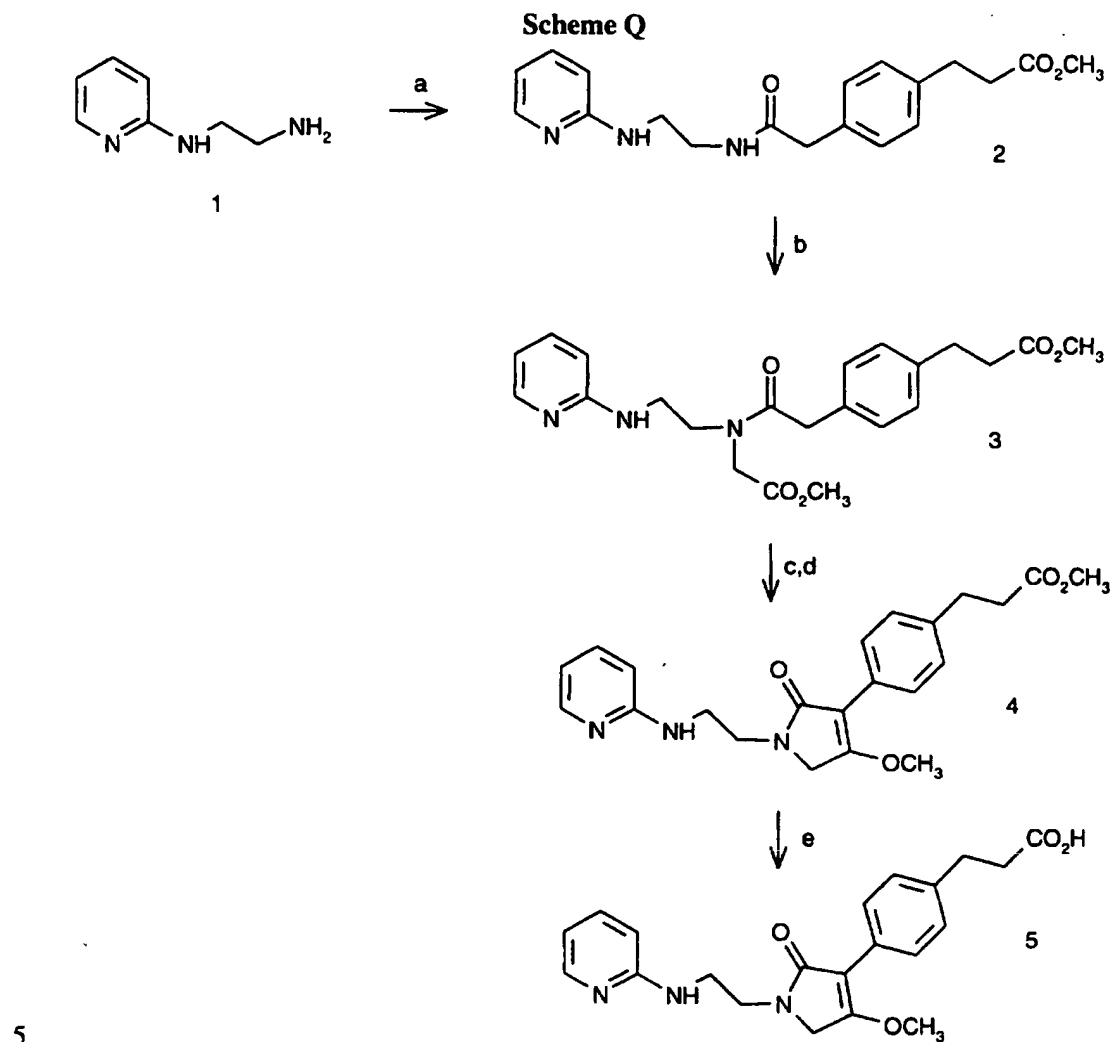


a) 4-[(6-amino-2-pyridinyl)methyl]phenol, Cs_2CO_3 , DMF; b) 1N NaOH, CH_3OH .

Compound **P-1**, prepared as described by Himmelsbach, *et al.*, AU-A-86926/91,

- 10 Example VI(28), is treated with a suitable substituted phenol, such as 4-[2-[2-(pyridinyl)amino]ethyl]phenol, following the general method of Himmelsbach *et al.*, Example 3(51), to give **P-2**. The tert-butyl ester in **P-2** is hydrolyzed with 1N NaOH in CH_3OH to give **P-3**. Alternatively, the tert-butyl ester may be cleaved with TFA or HCl in a suitable solvent such as CH_2Cl_2 .

Scheme Q describes a method of preparing exemplary fibrinogen receptor templates described in Linz, *et al.*, EP 0567968.

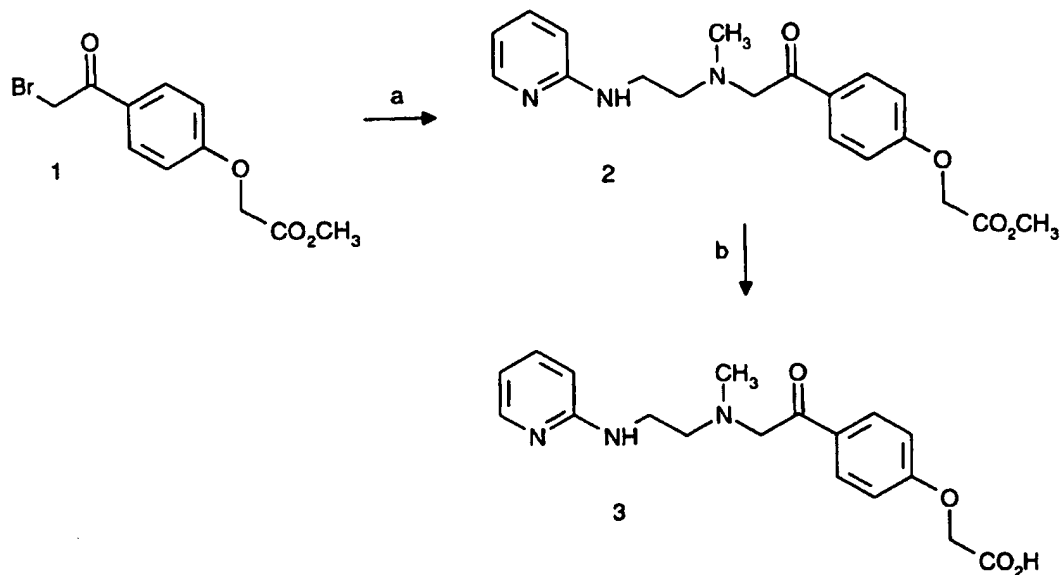


a) N-(2-pyridinyl)ethylenediamine, Ph_2POCl , Et_3N , DMAP, THF; b) NaH, $\text{BrCH}_2\text{CO}_2\text{CH}_3$, DMF; c) KOtBu , CH_3I , DMF; e) LiOH , H_2O , THF.

Following the procedures of Linz, *et al.*, EP 0567968, except substituting N-(2-pyridinyl)ethylenediamine for 4-cyanoaniline, gives Q-5.

Scheme R describes a method of preparing exemplary fibrinogen receptor templates described in Wayne, *et al.*, WO 94/22834.

Scheme R



a) N-methyl-N'-(2-pyridinyl)ethylenediamine, CH₃CN; b) 1N NaOH, CH₃OH

- 10 Following the procedures of Wayne, *et al.*, WO 94/22834, Example 1-2, except substituting N-methyl-N'-(2-pyridinyl)ethylenediamine for 1-(4-pyridyl)piperazine gives R-3.

Scheme S describes a method of preparing exemplary fibrinogen receptor templates described in Wayne, *et al.*, WO 94/22834.

Scheme S